Desmosome

Desmogleins and Desmocollins as Adhesive Molecules

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Following the identification of desmoglein and desmocollins as the transmembrane components of the desmosome, sequence analysis revealed that they are members of the cadherin family of cell–cell adhesion molecules. Cadherins are characterized by the presence of conserved extracellular calcium-binding motifs. Like the classical cadherins (e.g., E-cadherin), desmogleins and desmocollins each have five extracellular cadherin motifs. Within the most amino-terminal repeat, cadherins possess a tripeptide motif that has been shown to be critical for cell adhesion (Blaschuk *et al*., 1990). In classical cadherins, the motif is HAV (histidine/alanine/valine), whereas in desmocollin and desmoglein, it is YAT and RAL, respectively. Even though desmosomal cadherins resembled the classical cadherins at the amino-acid level, it had not been demonstrated that they were functional cell–cell adhesion molecules in their own right. Classical cadherins had been shown to promote aggregation when expressed in normally non-adherent, cadherin-null cells (mouse L-cells). Interestingly, expression of each desmosomal cadherin alone was not sufficient to confer cell–cell adhesion on L-cells, suggesting that a higher order organization was required for desmosomal cadherins to mediate cell–cell interactions.

Two studies (Marcozzi *et al*., 1998; Tselepis *et al*., 1998) used the cadherin-null L-cell system to demonstrate that desmosomal cadherins function as cell–cell adhesion molecules. Unlike the classical cadherins, desmosomal cadherins required coexpression of both desmoglein and desmocollin to generate strong cell–cell adhesion. As both desmosomal cadherins were required, it would suggest that the desmosomal cadherins may interact in a heterotypic manner. Homotypic as well as heterotypic interactions have been demonstrated *in vitro* using recombinant fragments of desmoglein and desmocollin (Syed *et al*., 2002). The heterotypic nature of this interaction was also observed *in vivo* using HT1080 cells (Chitaev and Troyanovsky, 1997). Interestingly, expression of the desmosomal plaque protein, plakoglobin, in cells expressing the desmosomal cadherins greatly increased cell aggregation. Taken together, these data suggest a model whereby desmogleins and desmocollins cooperate at the cell surface to generate cell–cell adhesion and plakoglobin functions to stabilize the extracellular interaction.

Calcium dependence is a hallmark of the cadherin family of cell adhesion molecules. In cells expressing the desmosomal cadherins, cell aggregation was inhibited by the addition of 5 mM ethylene diamine tetraacetic acid (EDTA), thus confirming the calcium dependence of the desmosomal cadherins. Tselepis *et al*. (1998) went on to demonstrate that desmosomal cadherin-mediated adhesion could be blocked by adding peptides that correspond to the cell adhesion recognition site of desmoglein or desmocollin.

Establishment of desmogleins and desmocollins as the mediators of desmosomal cell–cell adhesion was an important step in understanding the function of this cellular junction. These studies revealed that, unlike the classical cadherins in the adherens junction, desmosomes require expression of two desmosomal cadherins to generate a functional adhesive force. In addition, linkage of the desmosomal cadherins to the cytoskeleton through plakoglobin greatly increases the adhesive strength. These findings have proven to be the basis for understanding the mechanisms of desmosomal adhesion in various disease processes, including tumor progression and during development. More importantly, this work provides the framework for future studies that will focus on mechanisms regulating desmosomal adhesion in epithelial tissues.

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